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CONCERNING PHYSIOLOGICAL INVESTIGATIONS IN IMMUNOLOGY

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[Summary: Although Ado by no means underestimates the action of antigens and toxic agents on the nervous system, he criticizes the concepts of nervism, particularly those adhered to by Speranskiy's school, as far as understanding of immunity as a reflex process or a series of reflex processes is concerned. He particularly objects to the idea that individual nerve receptors show an individual and selective response to different antigens, depending on the location of the receptor in the body, and expresses the opinion that antigens may exert their action on any section of the peripheral or central system or any cell and tissue irrespective of its location.]

During recent years, the efforts of many pathophysiologists and immunologists in the USSR were concentrated on the elucidation of the physiological regularities governing the action of various antigenic substances, toxins, and viruses on the animal organism in connection with the relationships underlying the pathogenesis of infection processes and of the mechanism of immunity.

An interesting line of investigation in research on immunological problems was launched by P. F. Zdrodovskiy, who was shown that a study of the reactions of the organism to autogenic irritations from the point of view of general physiology makes it possible to discern in these reactions the laws governing the interrelationship between excitation and inhibition which have been established by N. Ye. Vvedenskiy. The applicability of Vvedenskiy's theories to phenomena of allergy has been pointed out before.

The problem in regard to the application of general physiological relationships to the interpretation of immunological phenomena is being studied at the Kazan' Institute of Vaccines and Sera. Thus, Volkova-Vorzunina (1952), who has studied in detail the nature of immunological reactions (formation of the antitoxins effective against diphtheria and tetanus) in horses used as producers of the antitoxins, found that these animals exhibit two types of reaction: the excitation type and the inhibition type. Alatyrtseva (1953) subjected to study the additivity of the immunizing action of the toxins of B. perfringens and B. histolyticus in rabbits upon combined immunization with both toxins. The quantity of antibodies active against each toxin was, in this case, larger than on immunization with each of the two toxins separately.

As distinguished from the approach typical for the investigations mentioned above, another group of investigations concentrated on the action of antigens on the cerebral cortex. One may mention in connection with this that changes in the higher nervous activity which are specific for each kind of antigen (toxin) could not be observed. Any changes which occur under the effect of bacterial exotoxins (Gorsheleva), endotoxins (Kotlyarevskiy), viruses (Zeytlenok), or foreign proteins (Khosak) amount to the development of a more or less prolonged diffuse inhibition in the cerebral cortex, diminishing of conditioned reflexes which had developed earlier, and delay in the formation of new conditioned reflexes.

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A third area of physiological research in immunology is represented by the study of special nervous mechanisms which participate in making effective the pathogenic and immunogenic effects produced by microorganisms.

A special place in work along this line is occupied by research on the role played by the so-called nerve reception organs in the pathogenesis of infectious diseases and the mechanism of the development of a resistance against them.

The status of this problem at present requires comprehensive discussion, because simplified methods of investigation were used and premature conclusions made on the basis of the results obtained. On the basis of differences in the activity of antigens, depending on the site of their application, Speranskiy wrongly concluded that the participation of nerve receptor organs in making effective the pathogenic and immunogenic action of antigens was thereby established. Speranskiy's method of proving this assumption is based on the unproven postulate that the receptor organs of the body are as diverse in quantity and quality as the effector structures, i.e., the organs and tissues.

However, present knowledge of the receptors of organs and tissues indicates that the reception by them of various stimuli originating in the environment is limited principally by the range of adequate irritants which has been determined during the process of evolution and consists of effects which contribute to an adaptation of the organism to existence under the conditions imposed by the environment and aid the organism in protecting itself against harmful effects. Thus, the chemoreceptors of the carotid bulb are normally excited as a result of changes in the gas composition of the blood (hypoxia) or because of the presence of acetylcholine or poisons which inhibit oxidation in the receptor tissues. Unusual, nonadequate irritants (poisons) first bring about quantitatively reinforced excitation and then destruction of the receptor apparatus. The range of irritations which bring about certain reflex responses is different for different species of animals.

The response to the action of antigens does not correspond by far to the capacity of receptor organs to become irritated as a result of contact with the antigen in question. A good example is the effect of various antigens (allergens) on the mucous membrane of the nose (Khansel' et al). The diverse nature of the sensitzation effects produced by these antigens has no connection with any specific action produced on the highest chemoreceptor apparatus in this region, i.e., the endings of olfactory nerves. It has been established that the objects on which these antigens act are not the endings of the olfactory nerve, but the epithelium of the mucous membrane of the upper respiratory tract, the endings of the trigeminus nerve, and the vascular-motor innervation of the region in question. In an allergy, interference with the sense of smell is a secondary effect due to inflammation.

When the assertion is made that differences in the pathogenic effect produced by the causative factor, depending on the site of its action, are due to differences in the receptor organs located in the parts of the body that are affected, the differences in metabolism within various organs are disregarded. These differences in metalbolism have a strong effect on the formation of the toxin and the binding of toxin which has formed or has been introduced from the outside. For instance, it has been established recently that the toxin of B. perfringens is bound by the tissues of the skin

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to a greater extent than by the tissues of the skeletal musculature or of the brain, while in the heart it is bound much more strongly than by the tissues mentioned above. One must add to this that there are differences in the blood circulation and lymph circulation and also in the permeability of capillaries in different tissues and different parts of the body. It is also pointed out that differences in the toxic and infectious effect depend on the degree of denervation of the region where the microorganism or toxin is introduced. However, these differences do not prove the significance of receptors, but rather the effect of changes of metabolism in the denervated tissue on the formation of the toxin and development of the pathogenic effect produced by the toxin.

The considerations outlined above emphasize that the method of investigating the role of nerve-receptor organs by comparing the pathogenic effects of the causative factors, depending on the site of its introduction into the organism, is faulty and that the problem requires a more precise physiological method for its clarification.

The results obtained by using the second approach also do not confirm the assumption in regard to the existance of special nerve-receptor organs in every part of the organism or the assumption that there is a specific action of antigens on nerve receptors of the organs and tissues. For instance, Bagramyan has shown that the toxic substances of the influenza virus (the Puerto Rico strain), when applied in the form of an emulsion prepared from the lungs of infected mice, produce changes in (i.e., an increase of) the sensitivity of the sensory nerve endings of the trigeminus and the vagus to irritation with carbon dioxide in mice and ferrets after the upper respiratory tracts of these animals have been irrigated with the emulsion. The reinforcement of a certain reflex effect connected with the respiration is also observed. When the animals are infected with influenza, the reflex mentioned above is suppressed. This reflex is restored after recovery of the animal. The effects described above are also observed, although to a minor extent, upon action on the mucous membranes of the upper respiratory tract of emulsions prepared from the lungs of uninfected mice.

Davis and Wright have recently (1954) established that the sensory neuron of the muscular and tendon reflexes is not acted upon by the tetanus toxin. The fact that under the effect of the tetanus toxin the electrical activity of the trunks of sensory nerves is increased, cannot be regarded as proof of the specific exciting action of the toxin on the sensory nerve endings, i.e., the exteroreceptors and proprioreceptors, because any irritation of a nerve results in an increase of its electrical activity. As far as the action of various antigenic substances on the interoreceptors (chemoreceptors) of the vascular reflexogenic zones is concerned, it has been established at present that in animals with an unchanged immunological reactivity different antigens exert a very weak irritating action on these receptors. In animals which repeatedly come in contact with antigens, the excitability of these receptors with respect to the specific antigens with which they came in contact and to other antigenic substances is increased. No selective and specific increase in the response of chemoreceptors to any one antigen could be obtained.

The question arises as to the nature of the reflexes resulting from the irritation of the chemoreceptors with antigens. According to our data, these are reflexes, the arcs of which are determined by anatomico-physiological characteristics of the connection of some reflexogenic zone with various effectors of the organism. In this manner the antigen may being about ordinary reflexes connected with the blood circulation,

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respiration, or other effectors identical with those that arise upon action on the receptors in question of irritants of a nonantigenic nature (electrical irritants, chemical substances, alkaloids, etc).

It has not been possible to establish that there are specific types of irritations and correspondingly specific reflexes originating at vascular chemoreceptors due to the action of antigens.

All this must be taken into consideration in work on the pathogenesis of infectious-toxic processes. The results that have been mentioned disaprove the existance of a specific nervous receptor for every antigen, as has been assumed by Speranskiy. The assumption that there is a specific topographic distribution of receptors which determines the pathogenic action of antigens is also wrong. During the process of evolution, the receptors have become differentiated and have reached a high degree of specialization in the sensory apparatus that responds to chemical stimuli in the organs of taste and smell of higher animals and humans. However, these organs are not very responsive to antigens and do not perceive fine differences in antigenic structure which would be capable of determining the character of the pathogenic and immunogenic action of these antigens. Different exteroreceptors and proprioreceptors as well as chemoreceptors of the blood vessels are excited by the antigens, but still do not reproduce the qualitative differences which are specific for the chemical structure of every antigen. The specific reaction is determined by the immunological relationships governing the reactions of globulin with the antigens.

The pathogenic action of bacteria, toxins, and viruses is not restricted by their action on the receptors. These agents also affect all divisions of the nervous system in addition to numerous other organs and tissues. The specific aspects of the disease are determined not only by the pathological reflex emanating allegedly from a specific receptor excited by a certain antigen, but are caused by a disturbance in the structure and functioning of many tissues and also interferences with the regulatory functions of a nervous system which has been injured by the infection.

The following examples illustrate this. Lately, we have been engaged in an investigation of the mechanism of the action of the botulinus toxin. It is known that this toxin is as much a true exotoxin as those of tetanus, diphtheria, etc. In botulism the nervous system is as much the principal objective of the action of the toxin as in tetanus. The question arises as to the place where the toxin injures the nervous system and at what point of application the disease begins after poisoning with the toxin. According to the data obtained by foreign investigators, this point of application corresponds to the action of the toxin on the efferent cholinergic synapses of the vegetative nervous system.

It is known that in poisoning with botulinus toxin, paralysis of the skeletal musculature, interference with respiratory motions, and interference with the blood circulation occupy a significant place. Death takes place as a result of a paralysis of the respiratory center 3-5 hours after introduction of the poison. On intravenous introduction of 0.0005 milligrams of this toxin in a cat, the symptoms of acute poisoning develop with 2-4 hours. These symptoms consist of paralysis of the skeletal musculature, short breath, tachycardia, dilation of the pupils, and exophthalmos. After introduction of the same dose of the poison into the thigh muscle, a paralysis develops only in the muscles of this thigh. Preliminary cutting of the anterior radices and the resulting elimination of the sensory innervation of the region in question do not prevent development of a local paralysis under the same experimental conditions. Later, an atrophy of the muscles of the extremity that has been affected develops, which testifies to the dystrophic effect of the poison on the muscular tissue of the extremity.

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A possible site of injury in the case described may be at the centers of the motor innervation in the spinal cord, because irritation of the poisoned muscle through the nerve brings about a normal contraction. One can hardly assume that the paralysis develops in this case by reflex action as a result of the resorption of the toxin from the muscle into the blood and the action of this toxin on the sensory nerve endings in other parts of the body, because then the dose of toxin needed for achieving the same result must be much higher than un intravenous administration because of the binding of a part of the toxin by the muscle tissues. Actually the dose of toxin necessary for bringing about local paralysis is equal or smaller than that needed in intravenous application; for that reason the point of application of the action of the toxin cannot be far beyond the limits of region immediately affected.

Analogous conditions are encountered in the study of the action of botulinus toxin on the heart of warm-blooded animals (Mikhaylov). On intravenous administration the toxin brings about a regular and consistent interference with the cholinergic innervation of the heart. Initially, the negative inotropic effect obtained in response to an irritation of the vagus in the neck of rabbits disappears. Then the negative chronotropic effect is also eliminated. The aspects of the poisoning resemble those observed in intoxication with atropine. By comparing the responses to the direct irritation of the peripheral end of the severed nerve with the effect obtained in its reflex irritation, one finds that the reflex response on irritation of the central end of the severed nerve is removed considerably earlier than the effect produced by an irritation of the peripheral end of the vagus. Thus, within three hours after the poisoning of the rabbit, the reflex response to an irritation of the central end of the vagus disappears completely, while an irritation of the peripheral end of the severed vagus is still retained, although the threshold of the irritation has been lowered and the effect produced by the irritation is incomplete. The negative inotropic effect disappears and only the negative chronotropic action is retained. This clearly indicates that the action of the toxin is primarily applied at the source of the motor nucleus (trophic center) of the vagus. The following experiment made by Mikhaylov also confirms this assumption. If one of the vagi is cut in the neck of the rabbit prior to introduction of the toxin and the toxin is then introduced, the irritation of the peripheral end of this nerve against the background of a developed intoxication results in completely normal negative inotropic and chronotopic effects. It is known that the scission of the vagus in the neck ruptures the first neuron of the parasympathetic innervation of the heart. Thus, the separation of the axons of this nerve path on botulinus intoxication protects the vagal innervation of the heart. This indicates that the motor endings of the vagus in the heart are not the point where the action of the toxin is exerted, i.e., that the action of the toxin is not similar to that of atropine.

If we assume that the toxin acts on the cardiac receptors, we may expect that introduction of the toxin into the tissue of the heart itself (at the tip of it or in the region where the venae cavae connect with the heart) will bring about a more rapid development of changes in the cholinergic innervation which has been mentioned above. It was found that the progress of changes in the nerve on poisoning of the animal by administering the toxin into the tissue of the heart not only does not proceed more rapidly than that taking place on poisoning of the animals through the blood, but even lags behind the latter. The question arises as to whether these findings can be interpreted as a

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consequence of the action of the harmful agents (toxins or alkaloids) on the receptors only, while changes in the cardiac activity should be regarded as a reflex similar to that which takes place upon action on the organism of adequate physiological irritants. It is obvious that we are encountering here breaks of the nervous system both in its central and peripheral (motor) links. The pathological reflex on the heart under conditions of poisoning with botulinus toxin represents a reflex taking place in a poisoned, injured, and modified nervous system.

Analogous results were obtained by Caranina (Kazan') in research dealing with the action of the dysentery toxin on the vagus innervation of the heart of dogs. The fact that the toxin of B. botulinus exerts a central and automatic (according to I. P. Pavlov) action is also confirmed by Abrosimov's experiments. Abrosimov investigated in our laboratories the action of this toxin on the reflex regulation of respiratory movements. Under the action of the toxin, the reflex inhibition of respiratory movements due to an irritation of the central end of the vagus is subjected to phase changes: the reflex is activated first and then inhibited.

At my suggestion, Alatyrtseva (Kazan') investigated the action of the tetanus toxin decerebration rigidity. She demonstrated that under the effect of the intoxication the rigidty continues longer and is more pronounced. She also demonstrated that the tetanus toxin is capable of inducing a contraction of the innervated skeletal muscle and of lowering in a pronounced manner the sensitivity of this muscle to acetylcholine. This indicates that there is a direct action of the tetanus toxin on the cholinergic processes taking place in muscle tissue. Thus, one may conclude that the action of the tetanus toxin is applied not only at the receptors but also at the nerve centers and the skeletal musculature and its myoneural connections.

Experiments by Medvedev, which have been carried out at our laboratory, convincingly demonstrate that one of the points of application of the pathogenic action of the influenza virus and of its toxin is the nerve cell and its synapsis with the axon of the neuron connected with this cell. Medvedev has shown that the influenza virus and its toxin have a significant influence on the synaptic transmission of impulses through the upper cervical sympathetic ganglion of cats. The action of an allantois culture of influenza (Shklyaver strain of the A type) brings about changes in the sensitivity of the ganglion to electric irritation of its preganglionic fibers and to acetylcholine and also a significant effect on the metabolism of the ganglion as far as the formation of the so-called mediators after excitation is concerned.

Introduction of an allantois culture of the influenza virus, which has a titer with respect to the hemagglutination reaction amounting to 1:640-1:320, brings about a sharp lowering of the sensitivity of the ganglion towards both electric irritation of its preganglionic fibers and the action of acetylcholine. The formation of the mediator and its elimination into the liquid perfusing the sympathetic ganglion cease entirely. When the titer of the virus which has been introduced is not very high (1:320 - 1:160), there is a state of the ganglion in which passage of an impulse through it after an electric irritation of the preganglionic fibers is still possible, although formation of the mediators does not take place. The test for the presense of the mediators was negative when the perfusate was introduced into the blood vessels of the upper cervical sympathetic ganglion of another animal.

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All the facts which have been cited indicate that there is a pronounced toxic action of the allantois culture of the influenza virus on the nerve cells of the upper cervical sympathetic ganglion. This raises the question as to whether the influenza virus and its toxin may function as stimulants of the nerve cells. In a special experiment which we conducted together with Medvedev, the effect of the allantois culture of influenza virus on the upper cervical sympathetic ganglion was tested upon application of a subthreshold electrical irritation to the preganglionic fibers. By this means we attempted to raise the sensitivity of the ganglion to the virus and its toxin, which according to our ideas are relatively weak macromolecular irritants of the nervous system. Our assumption in that respect was justified.

The action of the allantois culture of the influenza virus on the cells of the upper cervical sympathetic ganglion against the background of an irritation with an electric current regularly produced a contraction of the nictitating membrane (third eyelid) of the cat. This indicates that there is a direct excitation of the nerve cells of the ganglion by the virus and its toxin. After excitation of the ganglion in this manner, processes of inhibition develop in it. Its sensitivity to the electric current drops, and the phenomena of the toxic action of the virus develop. It is of interest to note that in actively immunized cats, neither an exciting nor a toxic action of the influenza virus could be detected, while the immunizing effect could not be ascribed to the action of antibodies accumulated in the blood, because the liquid with which the ganglion was perfused did not contain any antibodies.

The data cited above thus indicates that the pathogenic action of bacteria, their toxins, and their antigens is brought about not by their effects on receptors alone.

The specific nature of the pathogenesis of infectious diseases is determined by the diversity of the points at which the pathogenic action of microbes is applied in the nervous system and in other tissues. One must, of course, take into consideration that the syndrome of the disease is determined not only by local changes in the individual regions, but also by a disturbance of the regulation of functions caused by interference with the activity of the nervous system.

The problem in regard to the role of the nervous system in the mechanism of immunity to infection is being investigated at present along two different lines. The first line of investigation attempts a solution of the problem in regard to the role which conditioned reflexes play in the formation of antibodies while the second represents attempts to clarify the significance of nerve regulation of other physiological mechanism of protection that are not connected with the development of antibodies.

The theory of the reflex development of antibodies is a direct and logical extension of the theory in regard to the specific reflex nature of the development of the pathogenic action of bacteria in the organism. According to this theory, the antigen induces the formation of antibodies by acting on the receptors and by subsequent reflex transmission of a specific type of excitation of the nervous system to the cells which form antibodies.

This specific excitation transmits fully to the effector the characteristics of the chemical structure of the antigens and induces in them the formation of antibodies.

This theory of antibody formation represents a mechanical transference of the reflex principle to immunochemical processes. One must remember that the reflex regulation is possible only in the case of such functions (chemical reactions) which have become firmly established during the process of evolution in connection with some type of activity (e.g., contraction of muscles, secretion by glands). The reflex regulation of unusual functions, such as the transformation of normal globulin into immune globulin, is complicated by the circumstances that in this case the effector organ and the products of its activity are created anew depending on the antigen that has been introduced. This theory of the formation of antibodies has not been supported as yet by convincing factual data. Thus, in experiments by Ishikava and Friedberger (1923), the antigen was introduced into the tip of a rabbit's ear and the ear was cut off within several minutes. These investigators observed the formation of specific antibodies in the organism of the animal and assumed that the development of antibodies was a reflex action. At present it has been established with the aid of antigens labeled with tracer atoms that whenever the experiment is conducted in this manner, the antigen still has time to penetrate into the blood and to exert an ordinary immunizing action.

The errors committed by these two investigators were subsequently repeated by many others (Gordienko, etc). These researchers introduced antigen, B. coli, and other bacteria into the spleen and other regions of the vascular system which allegedly had been isolated from the blood circulation. They then concluded that they had observed the formation of antibodies by reflex action.

Checking of these results (by Pozdeyev and others) has shown that the antibodies appear in the organism only in cases when the antigen slips through into the general blood stream from the site at which it has been introduced.

Unfortunately the scientists who investigated the reflex formation of antibodies did not determine the antigen content in the blood of the experimental animals. In the experiments carried out to check the results of this research, it was established that in cases when the antigen is absent in the general blood circulation, there is no development of antibodies under the experimental conditions mentioned.

The data which are available at present lead to the conclusion that the specific transformation of normal globulin into immune globulin is an immunochemical process and takes place in the effector, i.e., in the cell of connective tissue. The nerve regulation of this process is brought about by influences exerted on the development of blood globulins, which serve as material for the formation of antibodies. This function has been firmly established during the process of evolution and the fact that it is subject to the regulating influence of the nervous system does not arouse any doubt.

Another important aspect of the influence of the nervous system on immunity is the nerve regulation of many nonspecific pathophysiological mechanisms of immunity. At present a great number of such mechanisms is known. It is sufficient to mention the functions exerted by the hormones of the suprarenal cortex, the significance of the sympathico-adrenal system as a regulator of oxidative processes, phagocytosis (Puchkov), and the activity of the barrier systems.

An undoubtedly important approach to the investigation of physiological mechanisms of immunity is the method of studying nonreactive immunity on smooth-muscle organs, which is being developed by Kravchenko.

The great significance of the superior cervical ganglia in the mechanism of the resistance of rabbits to poisoning with dysentery toxin is convincingly demonstrated by Pytskiy's experiments. The removal of both superior cervical sympathetic ganglia in rabbits, which are immune to diphtheria, sharply lowers their immunity to toxic doses of the vaccine (20 billion bacterial bodies), notwithstanding a considerable content of agglutinins in the blood which may amount to 1:3,200 — 1:1,600.

Zil'ber recently again called attention to the significance of processes of the elimination of bacteriophage and viruses from the organism through the kidneys and through other glands. A very detailed investigation of the indexes of elimination of bacteriophage by dogs was conducted under his direction by Parnes. The participation of the tubular apparatus in the elimination of bacteriophage by the kidneys of rats was demonstrated by Zobnina (Kazan'). In her experiments the filling of the tubular apparatus of the rat kidney with Trypan blue resulted in an increase of the elimination of bacteriophage. A definite influence on the elimination of the phage was also exerted in her experiments by poisoning of the kidneys with "floridzin."

Investigation of the phenomena of elimination immunity and of its nerve regulation is receiving, at present, increased and renewed attention on the part of immunologists. At my suggestion, Yafarova (Ufa) has investigated the processes of elimination of dysentery antigens in rabbits with a modified or nonmodified immunological reactivity. She has made the first attempt to apply the method of determining the coefficient of purification of the body from antigens in the case of colloidally dispersed antigens which have a molecular weight amounting to tens of thousands. The determination of the content of antigen in the blood and in the urine was determined in this case by means of the reaction of complement fixation carried out at low temperatures. She found that the coefficients of purification from dysentery antigens (Flexner dysentery) in normal rabbits, when there was an antigen content in the blood amounting to 1-3 mg %, was expressed, as is ordinarily the case for colloidal substances, by the very low figures, i.e., 0.013-0.105 ml/min. Compared with this, the coefficient of purification from autogenic creatinine, which is a nonthreshold substance for rabbits, is expressed by figures amounting to 5.535-8.8165 ml/min. The active immunization of rabbits with dysentery vaccine resulted in an increase of the coefficient of purification of the blood from dysentery antigens to 0.7[illegible] ml/min, while the coefficient of purification from autogenic creatinine remained almost unchanged (8.124 ml/min). This indicates that the processes of the reabsorption of the molecules of the antigen in the tubular apparatus of the kidneys are inhibited under the conditions of active immunization. By comparing the elimination of dysentery and typhoid antigens in rabbits which are immune to dysentery, it has been established that the typhoid antigen is eliminated in much smaller quantities. This indicates that special significance must be attached to the elimination of antigens by the kidneys as one of the physiological mechanisms for the protection of the organism against overloading or against a condition of the blood resulting from the destruction of bacteria by antibodies and phagocytes. Reznik (Kazan') also investigated the elimination of dysentery antigens by the kidneys of patients suffering from dysentery. He observed changes in the elimination of these antigens depending on the phase and stage of development of the disease.

Titova (1954) made the observation that the elimination of the influenza virus with the urine of dogs, after active immunization of the animals with the virus, increases in comparison with the elimination by nonimmunized dogs.

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Bashirova (1953) investigated, at my suggestion, the elimination of dysentery antigens with the saliva of dysentery patients. She established that the dysentery antigens is regularly eliminated with the saliva in a quantity amounting to 0.2 — 3.2 micrograms (gamma) per milliliter. The content of this antigen in the blood and in the saliva depends on the time and space elapsed since the beginning of the disease and the acuteness of the clincial courses of the disease. In almost 50% of the cases the content of the antigen in the saliva was higher than in the blood, which indicates that there is an intensive secretion of the antigen by the salivary glands. Upon recovery the antigen disappears from the saliva. It is of interest to note that in dysentery patients the antigen can be detected in the blood and in the saliva between the recurrences. The determination of the antigen may thus serve as an additional method for the diagnosis of chronic dysentery.

Khomyakov and Kolchurina (Kazan') have shown that the elimination of diphtheria toxin with the urine (0.5 AE [AYe = antigen units?] per milliliter) in guinea pigs can be observed twenty-four hours after introduction subcutaneously of 10 milliliters of an anatoxin containing 30 AE per milliliter.

Introduction of the toxin together with alum, egg albumin, or calcium chloride delays the absorption of the toxin into the blood and, consequently, its elimination with the urine. Thus, the elimination of the anatoxin with the urine reflects its movement and metabolism in the organism of the intoxicated animal. The purification of the organism from the toxin depends on the rate of its transport into the blood.

The new and more exact physiological methods of investigating processes of elimination of bacterial antigens, toxins, and viruses open up perspectives for a reevaluation of the problem in regard to the significance of elimination processes in immunity. The data which have been listed testify to the many ways in which the processes of the interaction of the organism with bacterial antigens, toxins, and viruses can be subjected to investigation by means of physiological methods. However, the application of precise physiological techniques of investigation in immunology is only in its infancy.

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